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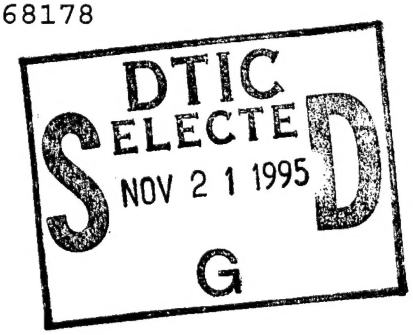
TITLE: Genetic Counseling Using BRCA-1-Linked Markers

PRINCIPAL INVESTIGATOR(S): Doctor Henry T. Lynch

CONTRACTING ORGANIZATION: Creighton University
Omaha, Nebraska 68178



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Omaha, Nebraska 68178

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13. ABSTRACT (Maximum 200 words)
Advances in molecular genetics have made it possible to identify individuals who have a strong inherited predisposition to breast cancer ovarian cancer. Because experience in genetic counseling of members of hereditary breast cancer families is exceedingly limited, we have mounted a study focusing on the genetic counseling process, with particular attention to the psychological impact and to adherence to recommended surveillance. To date, we have provided genetic counseling to 249 individuals from eight hereditary breast/ovarian cancer families. Of the 249 participants in the baseline (pre-counseling) telephone interviews (response rate to interviews - 77%), 75% of respondents opted to receive their BRCA1 test results. Using logistic regression analysis, we identified the following positive predictors of acceptance of testing: female gender (OR=5.0; CI=1.2-20.9), higher education level (OR=9.2; CI=1.2-70.7), and high baseline distress level (OR=7.8; CI=2.0-30.8). We observed significant improvement in knowledge from baseline to one-month follow-up for both carriers and non-carriers (F (time) = 47.2; p=.0001). By one month following counseling, female mutation carriers showed an increase in breast cancer worries, while non-carriers showed a decrease (F (time by group) = 4.6;p=.02). By six months, carriers had significantly higher scores on a depression measure (F=2.1;p=.04). We continue to accrue additional families and to evaluate the short- and long-term impact of BRCA1 testing.

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FOREWORD

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PI - Signature Date

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INTRODUCTION:

Advances in the molecular genetics of hereditary breast cancer have provided the heretofore unprecedented opportunity for DNA-based genetic counseling. This now enables physicians, in concert with certified genetic counselors, to delicately provide family members with information pertinent to whether or not they have inherited a cancer predisposing gene, and in our case this has involved BRCA1 and, ultimately will involve BRCA2 and p53.

These unheralded opportunities followed the work of Hall, et al. Hall et al. [1] who identified linkage of breast cancer susceptibility to the D17S74 locus (probe CMM86) on chromosome 17q21. Shortly after, linkage to D17S74 was confirmed in three of five families with hereditary breast/ovarian cancer (HBOC)[2]. An international consortium studying linkage to hereditary breast/ovarian cancer reported that 45% of site-specific breast cancer families [3] and 92% of families with HBOC syndrome were linked to BRCA1 [4]. However, none of the families with male breast cancer were linked to BRCA1. There is an increased risk for cancer of the colon and prostate in BRCA1 carriers.

A second gene, BRCA2, was mapped to chromosome 13 in 1994 [5]. The majority of families with cases of male breast cancer appear to be associated with BRCA2. BRCA2 confers a high risk of breast cancer, but not, it seems, for ovarian cancer. More research is needed with respect to the full tumor spectrum in BRCA1 and 2.

Easton et al. [6] estimate the frequency of BRCA1 mutant alleles to be 0.0007, based on 44 breast cancer deaths occurring among the relatives of 1203 women with ovarian cancer (31.8 expected). It is therefore likely that the frequency of carriers of BRCA1 mutations in the population is closer to one in 500. Ford et al. [7] estimate a cumulative risk of 48% to age 70 for ovarian cancer and 85% for breast cancer. However the data best fit a model with a mix of two susceptibility genes; one with a risk for breast cancer of 71% and for ovarian cancer of 87% to age 70 and a second gene with a risk for breast cancer of 86% to age 70 and a risk for ovarian cancer of only 18%. Little linkage data are available for apparent site-specific ovarian cancer, but a few rare families have been linked to BRCA1 [8].

Based on limited data, it appears that mutations can be identified in the coding region of the BRCA1 gene in over one-half of HBOC syndrome families. It is likely that mutations in the splice junctions, introns and regulatory regions of BRCA1 are responsible for most of the other families, but a small proportion will be unlinked. With this knowledge, it is now feasible to offer predictive testing based on BRCA1 gene analysis to women from HBC or HBOC families. Because of scientific, psychological, and social concerns, predictive testing programs are currently restricted to specialized research centers.

Lerman et al have conducted extensive research on the psychological

impact of cancer risk notification and adherence to cancer screening. She and her colleagues demonstrated that cancer risk notification can produce negative psychological consequences, including anxiety, traumatic stress symptoms, and impairment in daily functioning [9,10], and that distress can impair adherence to recommended surveillance [11-13]. While most of her work has focused on breast cancer, she has collaborated on studies of colon cancer risk and screening [11,14-16]. Her more recent work focuses on psychological issues in genetic testing for cancer susceptibility [17,18], including a recent study which showed that anxiety can interfere with comprehension of genetic risk information [19].

Goals and Objectives

The goals of our study are to identify the impact of genetic counseling in HBC and HBOC families where gene linkage to BRCA1 has been identified. This study is designed to demonstrate the feasibility of genetic counseling for HBC and HBOC, and to evaluate the impact of counseling on psychological state and medical behavior. The subject of genetic counseling in HBC and HBOC has never been systematically investigated in either a research or clinical setting. The study is also designed to examine predictors of those adverse consequences that could evolve from this genetic counseling. This information may enable physicians and genetic counselors to anticipate and prevent problems in individual clients.

BODY:

Eligible members of BRCA1-linked families receive an introductory letter, followed by a baseline, structured telephone interview administered by a trained interviewer at Georgetown University under the direction of Caryn Lerman Ph.D., a clinical psychologist/geneticist at Georgetown University, Washington, D.C.. About four weeks later, these individuals have an opportunity to attend an education session at which time information about gene linkage, hereditary breast cancer and surveillance measures are again reinforced prior to individual counseling to obtain genetic test results for breast-ovarian cancer susceptibility.

All genetic counseling and testing is provided by, and/or supervised by Dr. Lynch and his colleagues. Telephone interviews are conducted from Georgetown University at one-, six-, twelve-, and twenty-four months following genetic counseling to evaluate the impact of disclosure of genetic information.

Progress in our study of genetic counseling based on BRCA1 linked markers has been extremely well-targeted and productive. We have collected 319 blood specimens for DNA analysis from a total of 43 families. The DNA is used in the search for germline mutations, in collaboration with Steven Narod, M.D., of McGill University in Montreal, Canada, and Gilbert Lenoir, Ph.D., D.V.N., in Lyon, France.

To date, genetic counseling has been provided to eight HBOC families where BRCA1 germline mutations have been identified. Pedigrees of these eight families are shown in Figures 1-8 (see Appendix). The Table shows the family number, the date when the family was counseled, and the number of members who were counseled and provided with individual risk assessment in each of the eight families. The 43 well-defined HBC/HBOC families in our resource which have sufficient gene linkage and/or DNA mutation information available are eligible for counseling in the future. The most informative of these families are being set up with appointments for genetic counseling.

TABLE

Family Number	Date Family was Counseled	Number of Members Counseled
1234	August 20, 1994	21
1813	January 29, 1995	9
1816	August 19, 1995	16
1973	May 27, 1995	12
2090	February 18, 1995	10
2651	April 22, 1995	29
2770	March 18, 1995	32
3079	June 10, 1995	9

Individuals counseled since August 1, 1994 and the date on which they were counseled.

Since this grant was awarded we have identified 76 new breast cancer prone families. Of these, by pedigree analysis, 29 have

been diagnosed as consistent with HBC and 16 with the HBOC syndrome. Pedigrees of these families have been sent to Steven Narod, M.D. to determine eligibility for linkage analysis.

To date, a total of 249 individuals have participated in the baseline (pre-counseling) telephone interviews (response rate to interviews -77%). In terms of their demographic backgrounds, 100% of respondents are white, 69% are female, 88% have a high school education or greater, and 71% are employed. The average age or respondents is 43 +/- 14 years.

Thus far, about 75% of respondents have opted to receive their BRCA1 test results and 25% have declined. We conducted logistic regression analysis to identify predictors of acceptance of testing. Significant positive predictors include: female gender (OR=5.0; CI=1.2-20.9), higher education level (OR=9.2; CI=1.2-70.7), and high baseline distress level (OR=7.8; CI=2.0-30.8). Other factors have significant bivariate associations with uptake of testing include having health insurance and being more knowledgeable about hereditary breast cancer.

We have also conducted preliminary analyses of the impact of BRCA1 testing on psychological outcomes. Our data show significant improvements in knowledge from baseline to one-month follow-up for both carriers and noncarriers (F (time) =47.2;p=.0001). By one-month following counseling, female

mutation carriers showed an increase in breast cancer worries, while noncarriers showed a decrease (F (time by group)=4.6;p=.02). There were no significant differences between carriers and noncarriers in depression at one-month follow-up. However, by six months, carriers had significantly higher scores on a depression measure (F=2.1;p=.04). Increases in depression in the mutation carriers was predicted by specific coping strategies involving venting of feelings, information-seeking, and planful problem-solving.

CONCLUSIONS:

These preliminary data provide support for the feasibility of our ongoing research and the potential to elucidate clinically important information. However, since only a subset of the sample have been enrolled to date, it may be premature to draw conclusions from these data. Nonetheless, the following tentative interpretations may be made: (1) individuals who present for genetic testing are more likely to be female and to be more distressed about their risk. This points to the need to address patients' psychosocial concerns during the genetic counseling visit; (2) any adverse effects of genetic counseling may not be obvious in the short term. This underscores the need for long-term follow-up of participants in genetic counseling programs; (3) in the short term, coping strategies involving acceptance may be more beneficial than those strategies aimed at changing the situation. This points to possible avenues for

designing adjunctive psychological therapies.

Manuscripts relevant to this research are in preparation. One manuscript dealing with genetic counseling with attention to the reasons why about 25% of the members of these families decline participation in this DNA-based genetic counseling will be submitted to the New England Journal of Medicine, as it contains important public health implications. A second manuscript dealing with the psychological evaluation of the genetic counseling interviews on more than 100 BRCA1 positive and negative patients is also in preparation.

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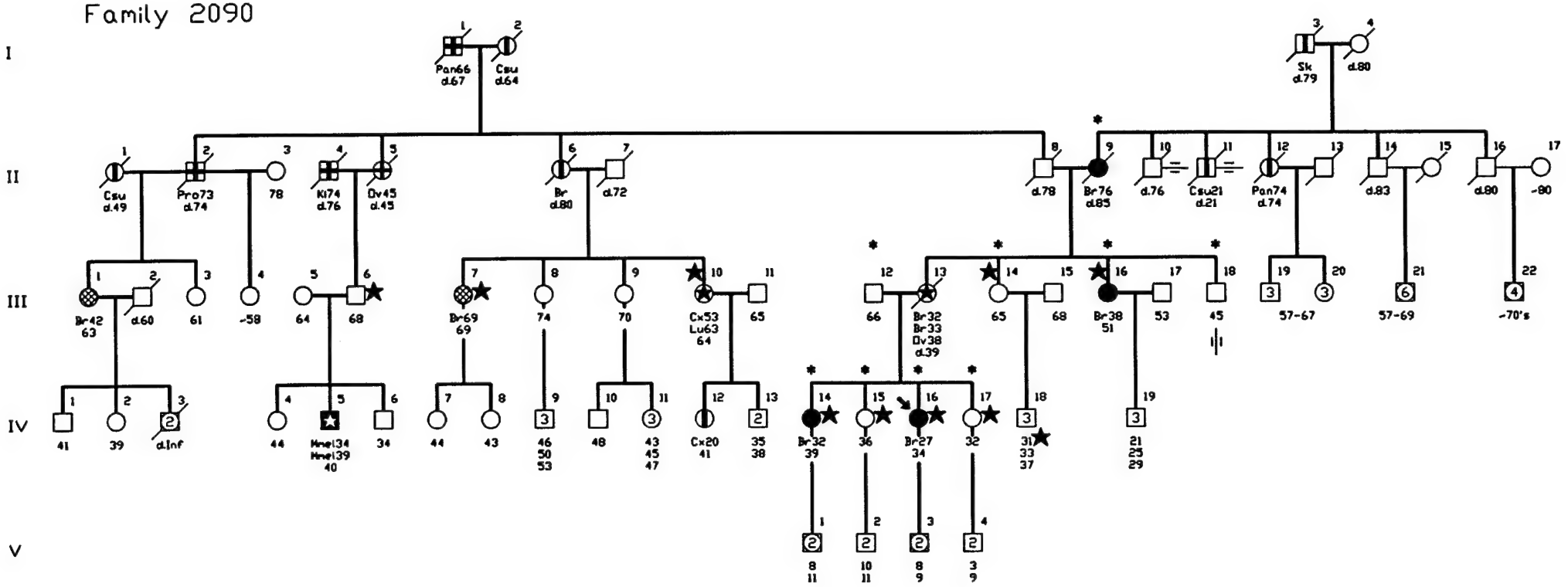
APPENDIX

Pedigrees of eight HBOC families where BRCA1 mutations have been identified.

Family 2090



LEGEND

Male 1 / Female 2	Individual number
28 / 33	Unaffected, Current age
Lu53 55 / Br45 47	Cancer by Pathology, age at diagnosis, Current age
d.54 / d.86	Cancer by Family History, age at death
	In-Situ Carcinoma by Pathology Report
	Multiple Primary Cancers Unverified
	Multiple Primary Cancers by Medical Records or Death Certificates
	Multiple Primary Cancers by Pathology
	Cancer by Death Certificate or Medical Records
4	Number of Unaffected Progeny (Both Sexes)
↘	Proband

Cancer Sites

Br	Breast
Csu	Cancer Site Unknown
Cx	Cervix
Ki	Kidney
Mmel	Malignant Melanoma
Ov	Ovarian
Pan	Pancreas
Pro	Prostate
Sk	Skin

* Blood Sampled

★ Counseled in 1995

01/13/1995
2090-2

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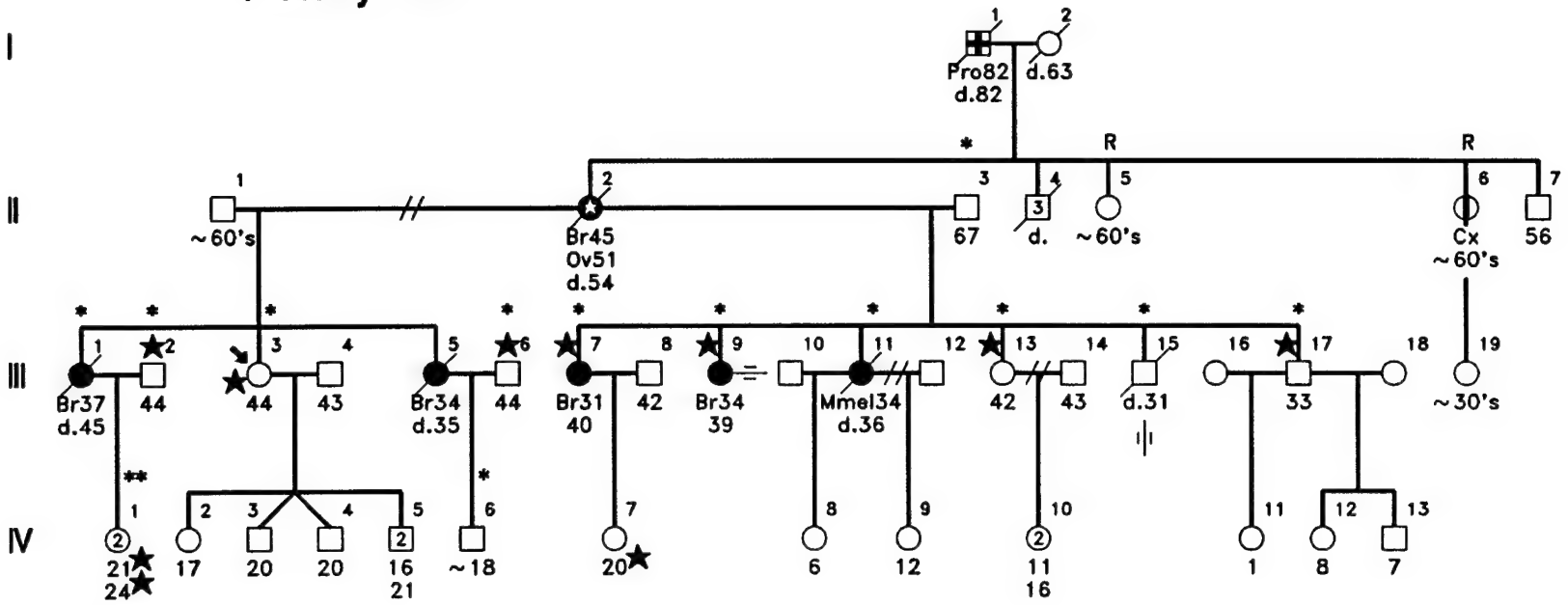
Family 1813



LEGEND

Male 1 / Female 2 — Individual number
Unaffected
28 / 33 — Current age

Lu53 55 / Br45 47 — Cancer by Pathology, age at diagnosis, Current age

d.54 / d.86 — Cancer by Family History, age at death

Multiple Primary Cancers Unverified

Multiple Primary Cancers by Medical Records or Death Certificates

Multiple Primary Cancers by Pathology

Cancer by Death Certificate or Medical Records

(4) — Number of Unaffected Progeny (Both Sexes)

Proband

Twins

Identical Twins

Cancer Sites

Br	Breast
Cx	Cervix
Ov	Ovarian
Pro	Prostate

* Blood Sampled

R Refusing

★ Counseled in 1995

01/19/1995
1813-2

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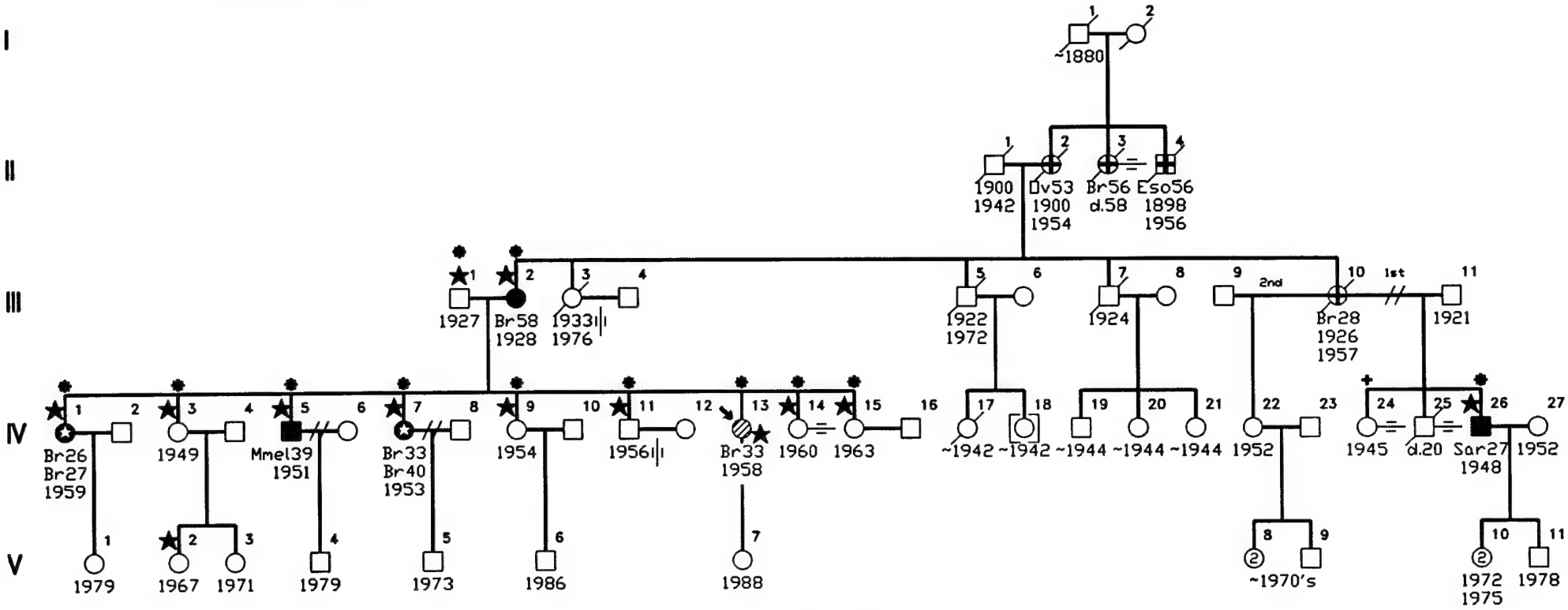
Family 1973



LEGEND

Male	Female	
1	2	Individual number
28	33	Unaffected, Current age
Lu53 55	Br45 47	Cancer by Pathology, age at diagnosis, Current age
		In-Situ Carcinoma by Pathology Report
d.54	d.86	Cancer by Family History, age at death
		Multiple Primary Cancers by Pathology
		Cancer by Death Certificate or Medical Records
[4]		Number of Unaffected Progeny (Both Sexes)
		Proband

Cancer Sites

Br	Breast
Eso	Esophagus
Mmel	Malignant Melanoma
Ov	Ovary
Sar	Sarcoma

- Blood Sampled
- \+ Blood Kit sent
- ★ Counseled in 1995

03/29/1995
1973GR-2

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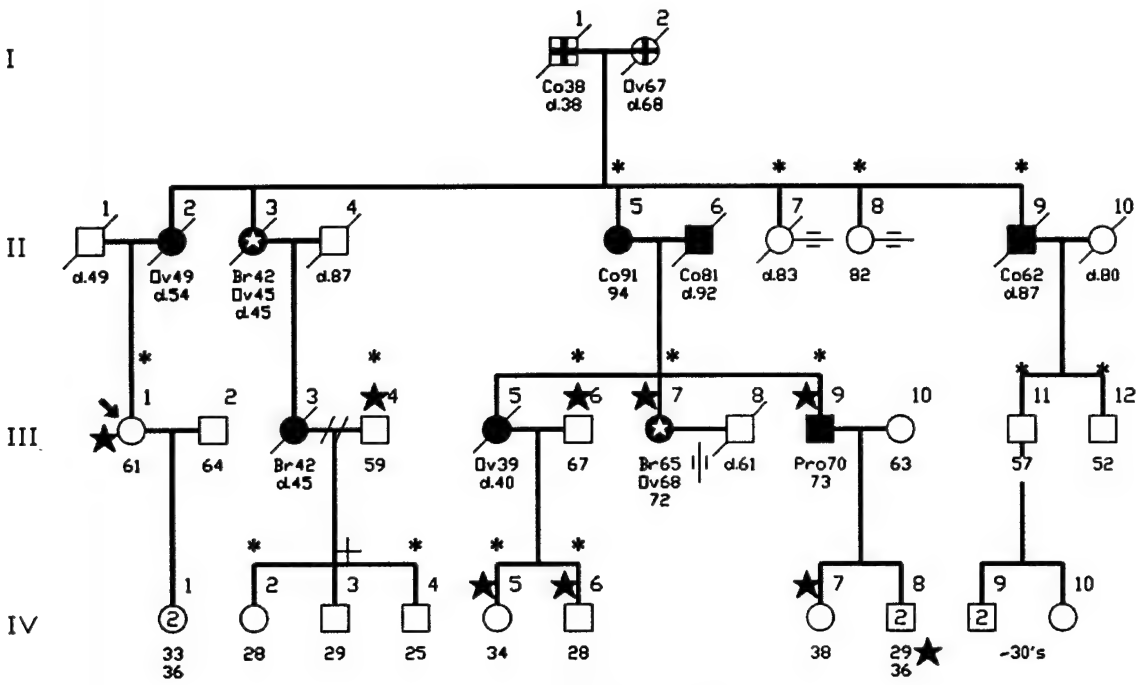
Family 3079



LEGEND

Male 1 / Female 2 — Individual number

Unaffected — Current age (e.g. 28, 33)

Cancer by Pathology, age at diagnosis — Current age (e.g. Lu53 55; Br45 47)

Cancer by Family History, age at death (e.g. d.54; d.86)

Cancer by Death Certificate or Medical Records

Number of Unaffected Progeny (Both Sexes)

Proband

Cancer Sites

Br	Breast
Co	Colon
Ov	Ovarian

★ Counseled in 1995

* Blood Sampled

\+ Blood Kit sent

06/06/1995
3079-3

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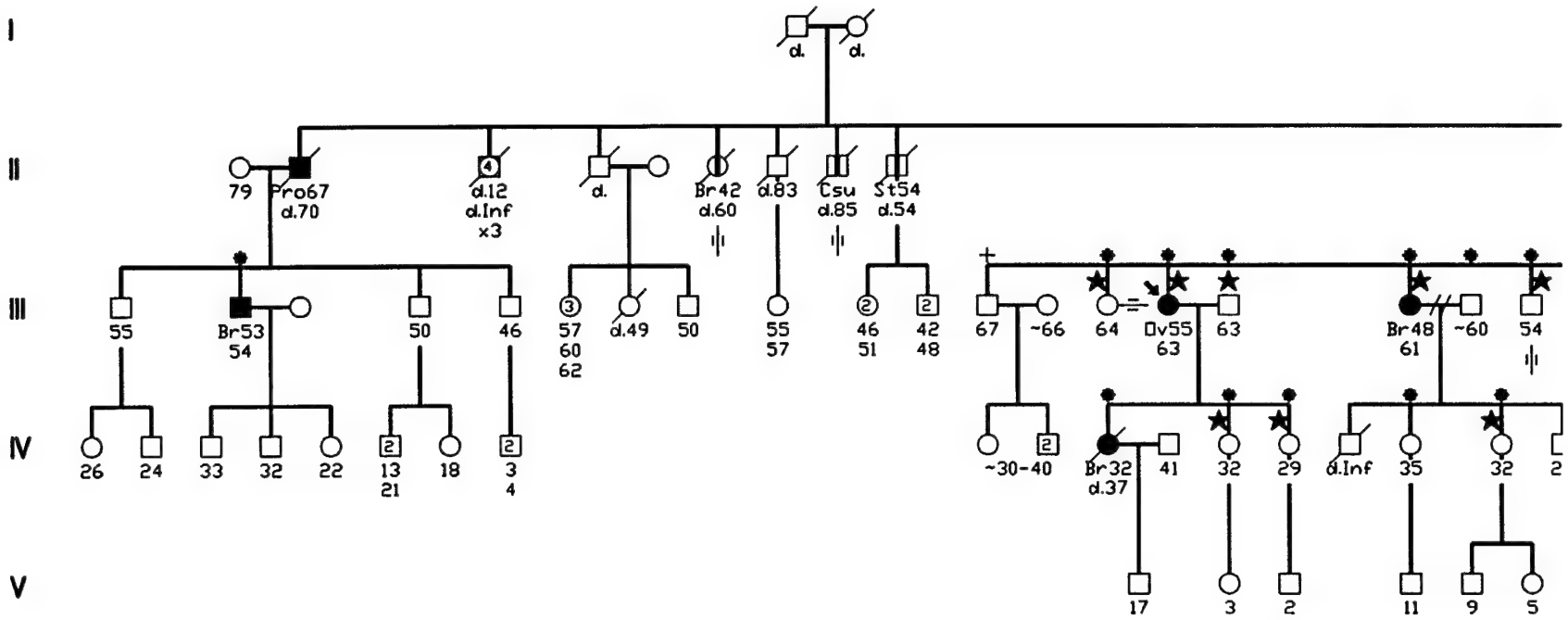
Family 2651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Br42
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d.83
Csu
d.85
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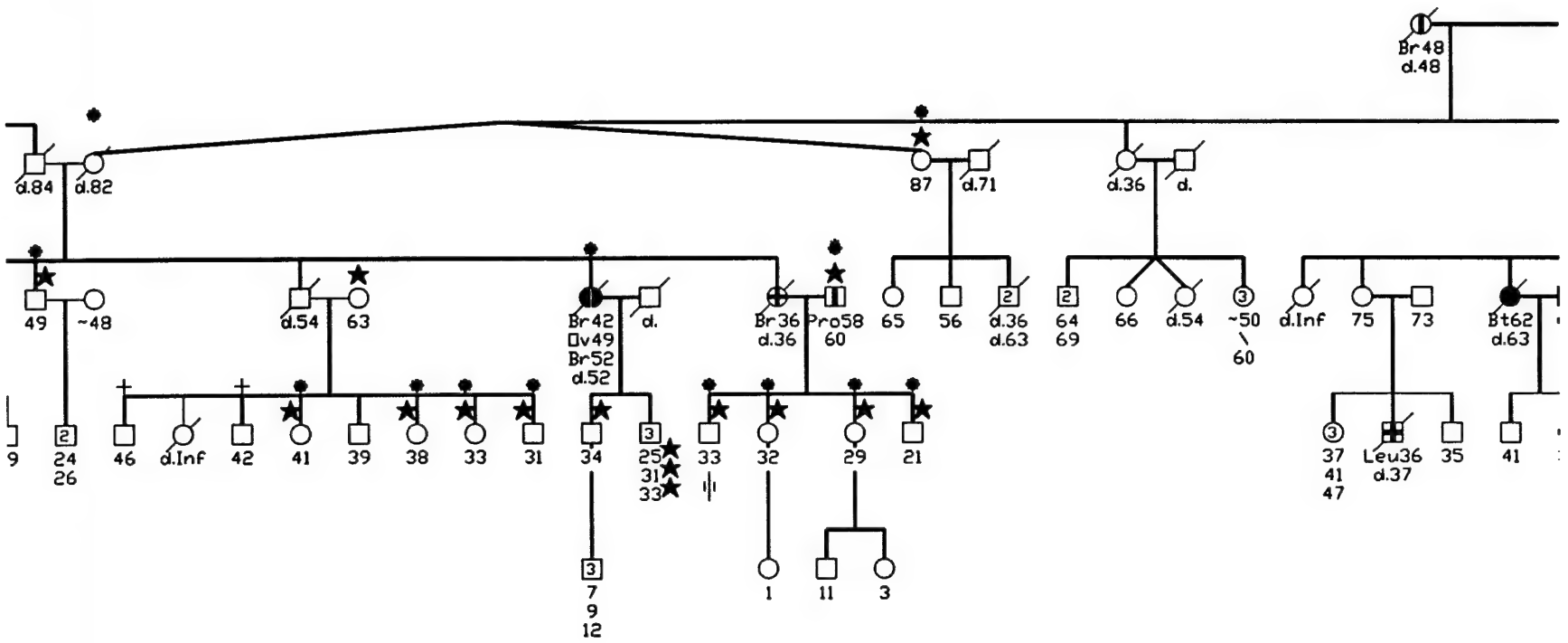
Family 2651



LEGEND

Male 1 / Female 2

- Individual number
- Unaffected — Current age (e.g. 28, 33)
- Cancer by Pathology, age at diagnosis — Current age (e.g. Lu53 55, Br45 47)
- Cancer by Family History, age at death (e.g. d.54, d.86)
- Multiple Primary Cancers by Medical Records or Death Certificates
- Multiple Primary Cancers by Pathology
- Cancer by Death Certificate or Medical Records
- Adopted
- (4) Number of Unaffected Progeny (Both Sexes)
- Proband
- Twins — Identical Twins

Cancer Sites

Br	Breast
Bt	Brain Tumor
Co	Colon
Csu	Cancer Site Unknown
En	Endometrium
Gb	Gallbladder
Ki	Kidney
Leu	Leukemia
Lu	Lung
Lym	Lymphoma
Ov	Ovary
Pan	Pancreas
Psu	Primary Site Unknown
St	Stomach

- ★ Counseled in 1995
- ● Blood Sampled
- \+ Blood Kit sent

04/20/1995
2651-6

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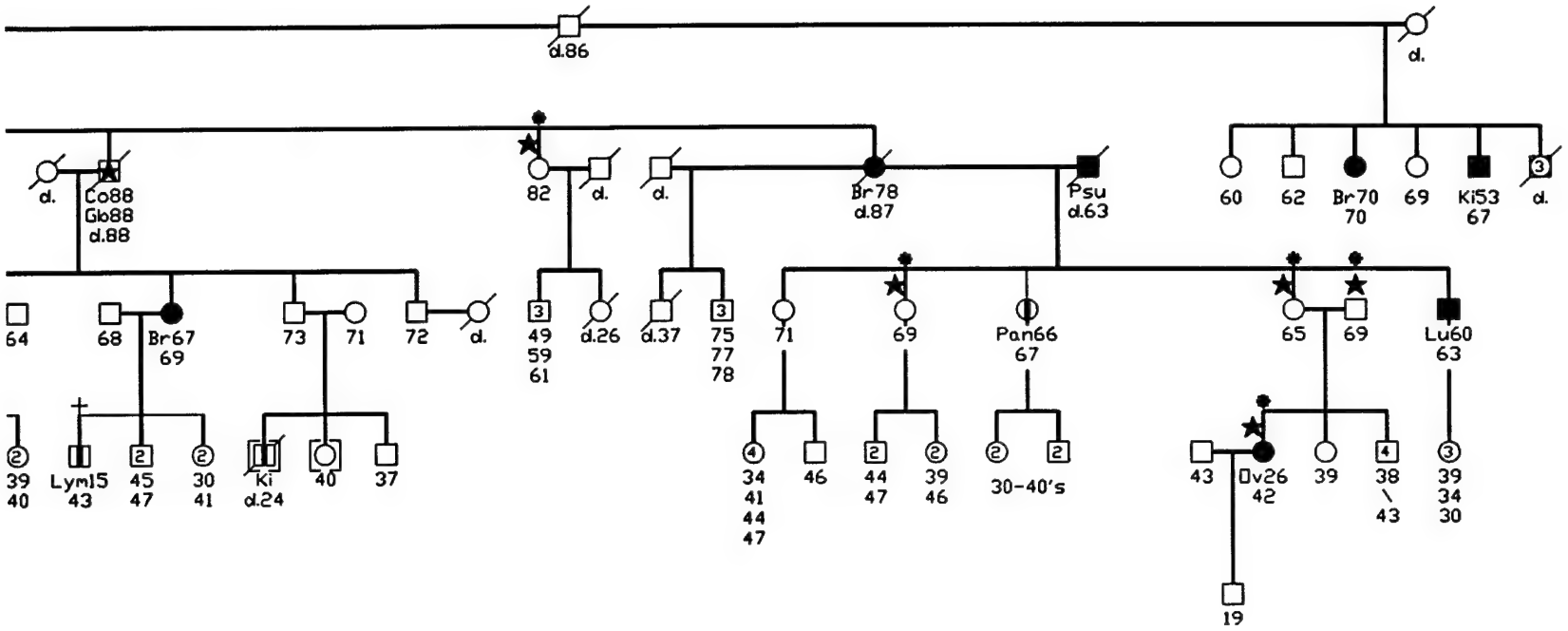
Family 2651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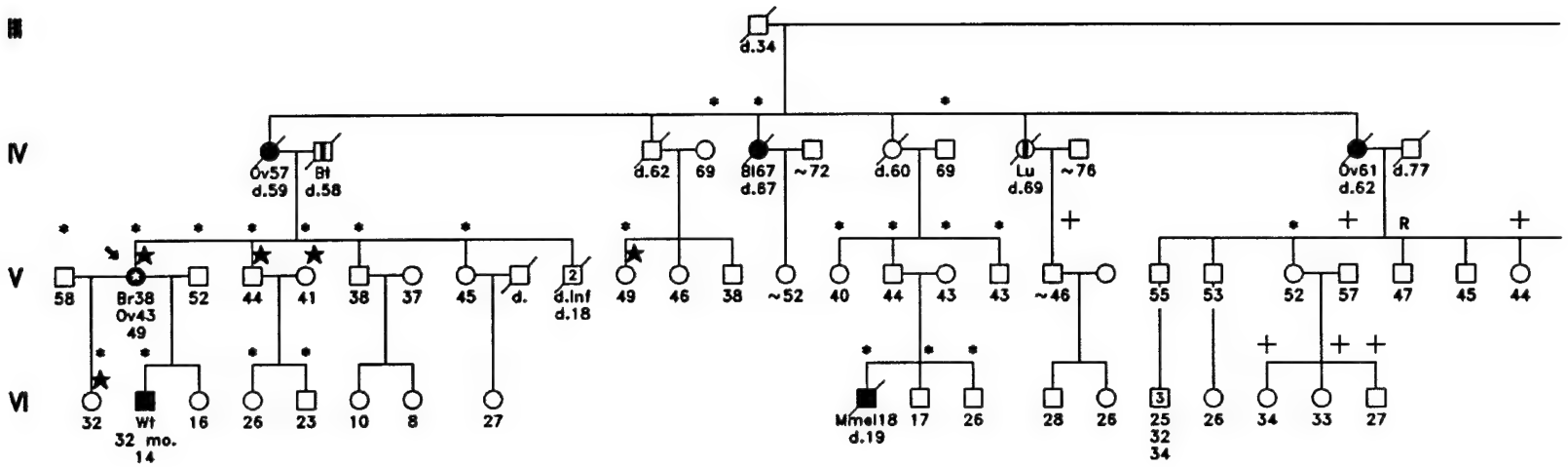
Family 1234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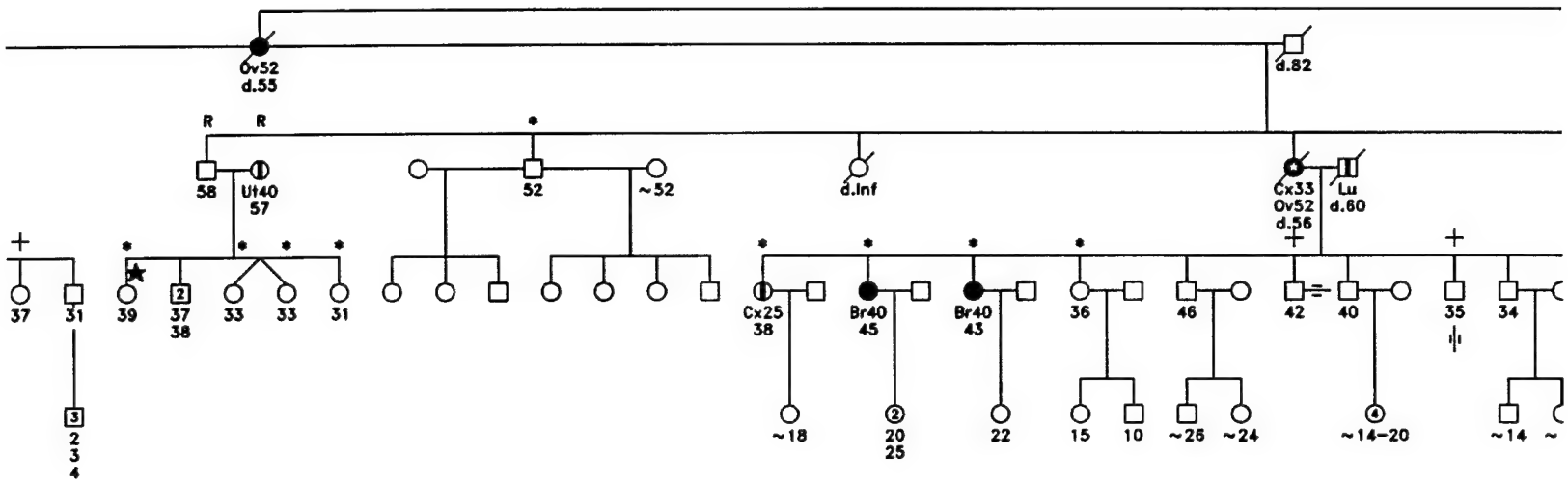
Family 1234



LEGEND

Male 1 / Female 2	Individual number
□ / ○	Unaffected
28 / 33	Current age
■ / ●	Cancer by Pathology, age at diagnosis
Lu53 55 / Br45 47	Current age
▨ / ⊘	In-Situ Carcinoma by Pathology Report
◫ / ◐	Cancer by Family History, age at death
d.54 / d.86	
⊠ / ✪	Multiple Primary Cancers Unverified
▣ / ✹	Multiple Primary Cancers by Medical Records or Death Certificates
★ / ✪	Multiple Primary Cancers by Pathology
▣ / ⊕	Cancer by Death Certificate or Medical Records
④	Number of Unaffected Progeny (Both Sexes)
↘	Proband

Cancer Sites

Br	Breast
Bt	Brain Tumor
Cx	Cervix
Fe	Female
LgBo	Large Bowel
Lu	Lung
Mmel	Malignant Melanoma
Mou	Mouth
Ov	Ovarian
Pan	Pancreas
Pro	Prostate
St	Stomach

+	Blood Kit sent
*	Blood Sampled
R	Refusing
★	Counseled in 1995

08/15/1994
1234YEL2

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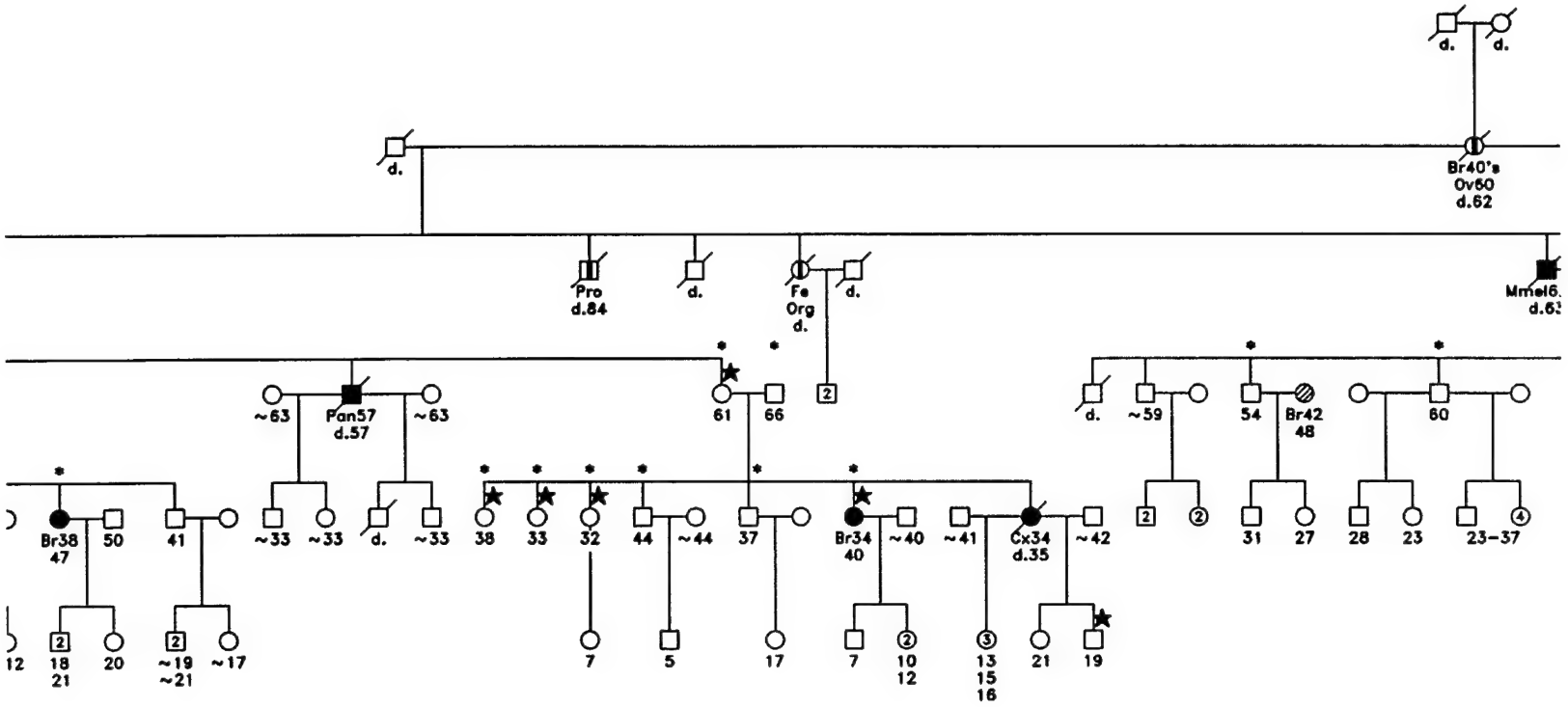
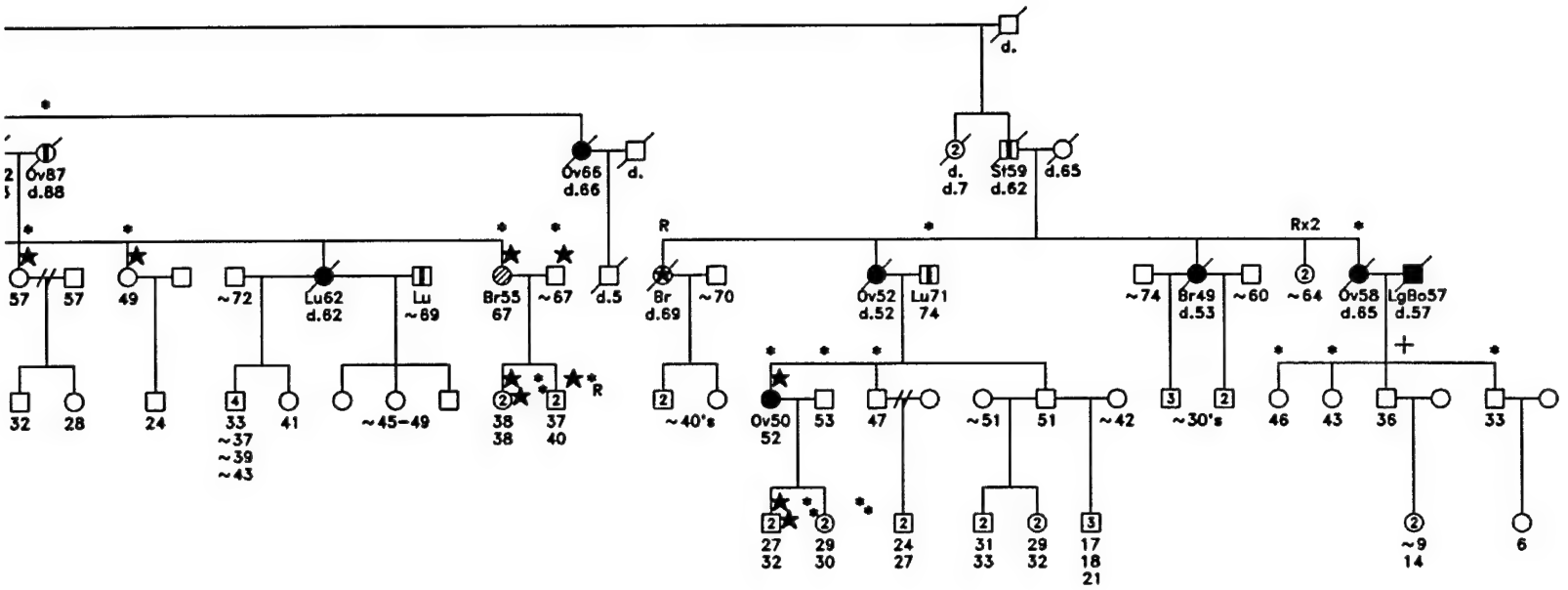
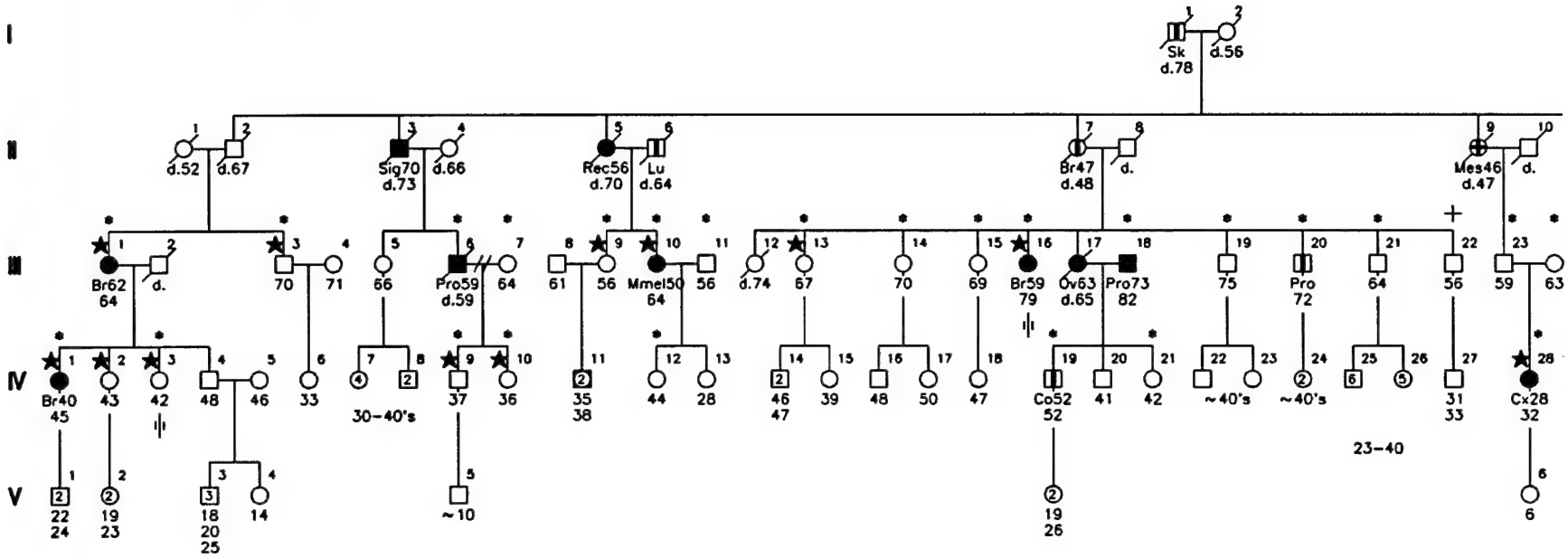
Family 1234


d.
d.
d.
Br40's
Ov60
d.62
Pro
d.84
d.
Fe
Org
d.
d.
Mmel6.
d.6
~63
Pan57
d.57
~63
61
66
2
d.
~59
54
Br42
48
60
Br38
47
50
41
~33
~33
d.
~33
38
33
32
44
~44
37
Br34
40
~40
~41
Cx34
d.35
~42
2
2
31
27
28
23
23-37
4
12
2
18
21
20
2
~19
~21
~17
7
5
17
7
2
10
12
3
13
15
16
21
19


d.
Ov87
d.88
Ov66
d.66
d.
d.
d.7
St59
d.62
d.65
R
Rx2
57
57
49
~72
Lu62
d.62
Lu
~89
Br55
67
~67
d.5
Br
d.69
~70
Ov52
d.52
Lu71
74
~74
Br49
d.53
~60
~64
Ov58
d.65
LgBo57
d.57
32
28
24
33
~37
~39
~43
41
~45-49
38
38
37
40
R
~40's
Ov50
52
53
47
~51
51
~42
~30's
46
43
36
33
27
32
29
30
24
27
31
33
29
32
17
18
21
~9
14
6

Family 2770



LEGEND

Male 1 / Female 2

- Individual number
- Unaffected; Current age (e.g. 28 / 33)
- Cancer by Pathology, age at diagnosis; Current age (e.g. Lu53 55 / Br45 47)
- In-Situ Carcinoma by Pathology Report
- Cancer by Family History, age at death (e.g. d.54 / d.66)
- Multiple Primary Cancers Unverified
- Multiple Primary Cancers by Medical Records or Death Certificates
- Multiple Primary Cancers by Pathology
- Cancer by Death Certificate or Medical Records
- Number of Unaffected Progeny (Both Sexes)
- Proband

Cancer Sites

Br	Breast
Co	Colon
Lu	Lung
Mes	Mesentery
Mmel	Malignant Melanoma
MNeu	Malignant Neurilemoma
Ov	Ovarian
Pro	Prostate
Rec	Rectal Colon
Sig	Sigmoid Colon
Sk	Skin

- ★ Counseled in 1995
- ▲ Tumor Tissue
- * Blood Sampled
- \+ Blood Kit sent

03/15/1995
2770-7

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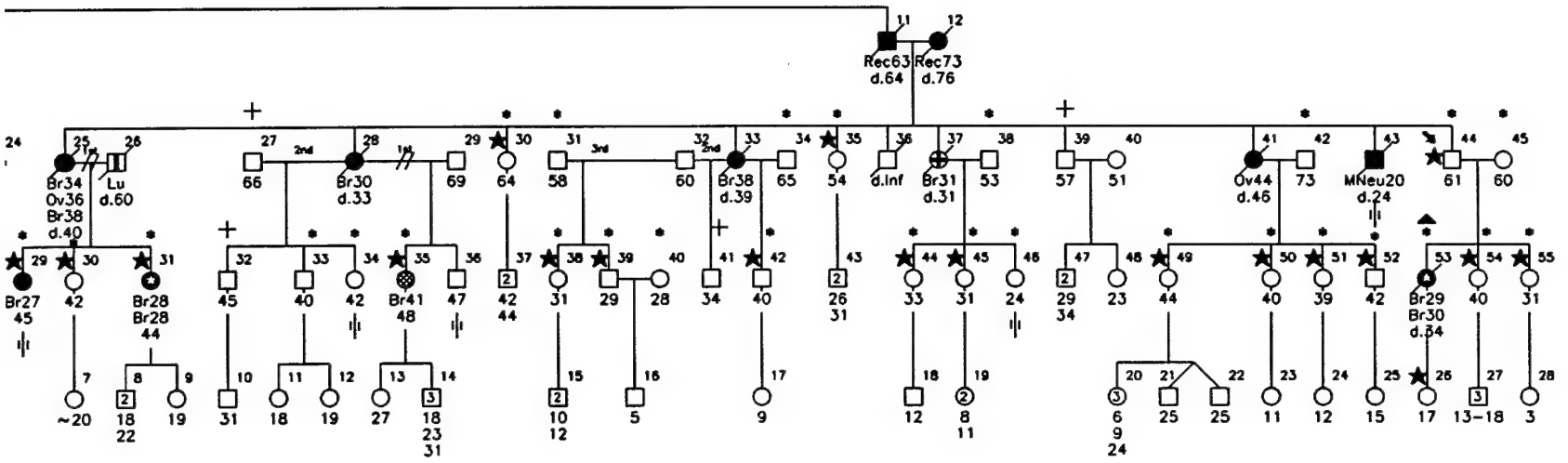
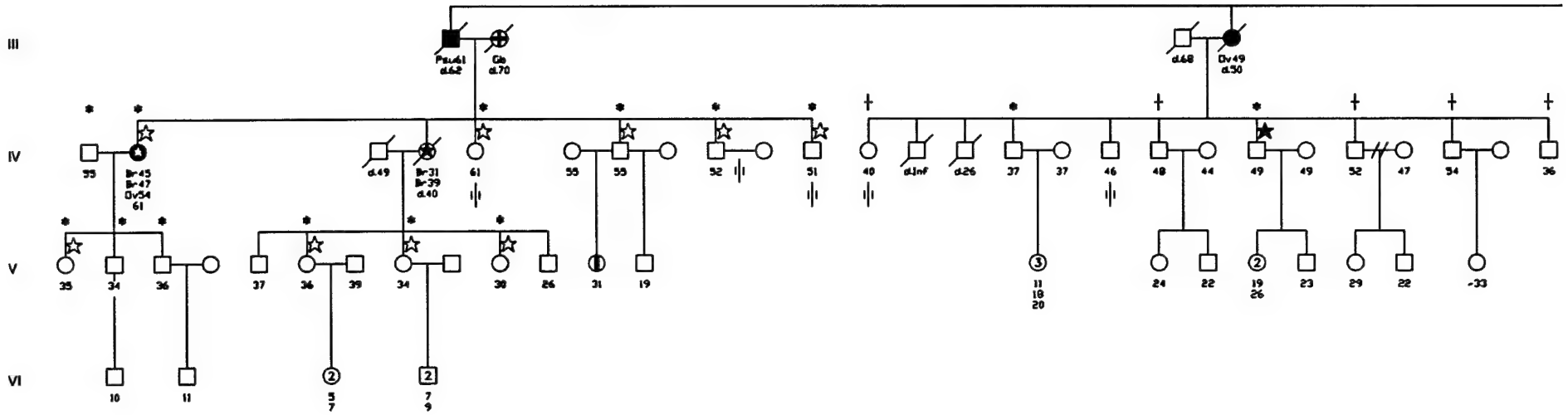
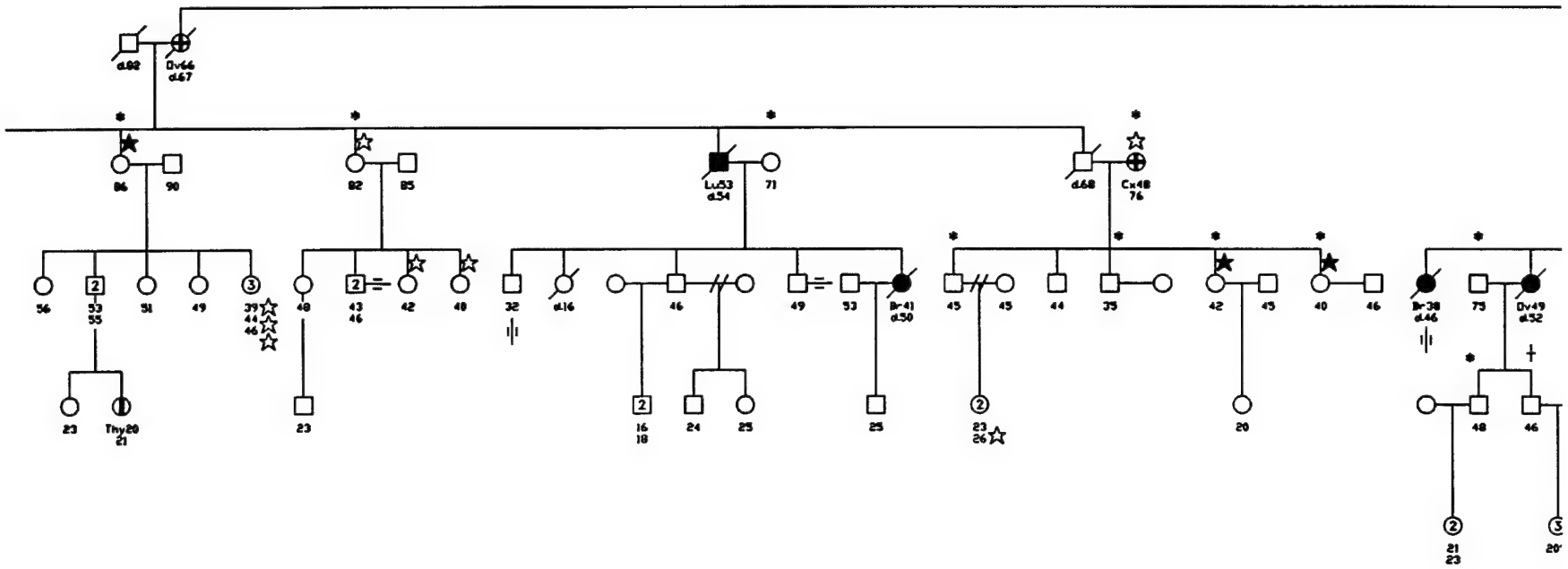
Family 2770


Rec63 d.64
Rec73 d.76
Br34 Ov36 Br38 d.40
Lu d.60
Br30 d.33
Br38 d.39
d.Inf
Br31 d.31
Ov44 d.46
MNeu20 d.24
Br27 45
Br28 Br28 44
Br41 48
Br29 Br30 d.54
~20
18 22
19
31
18
19
27
18 23 31
10 12
5
9
12
8 11
6 9 24
25
25
11
12
15
17
13–18
3

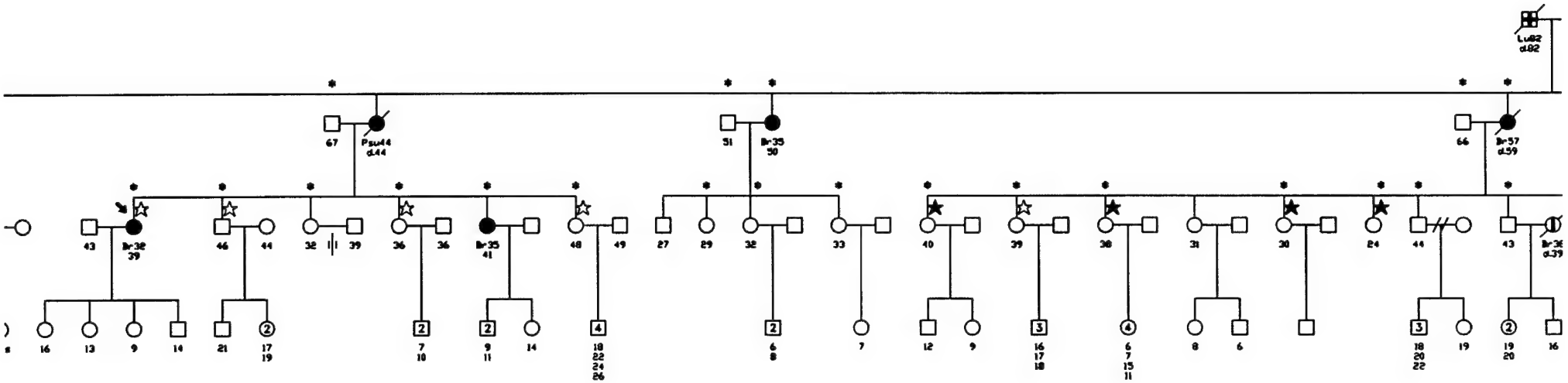
Family 1816


II
III
IV
V
VI
Pa.d61
d.62
Gb
d.70
d.68
Dv49
d.50
55
Br45
Br47
Dv54
61
d.49
Br31
Br39
d.40
61
55
55
52
51
40
d.Inf
d.26
37
37
46
48
44
49
49
52
47
54
36
35
34
36
37
36
39
34
38
26
31
19
11
18
20
24
22
19
26
23
29
22
-33
10
11
5
7
7
9

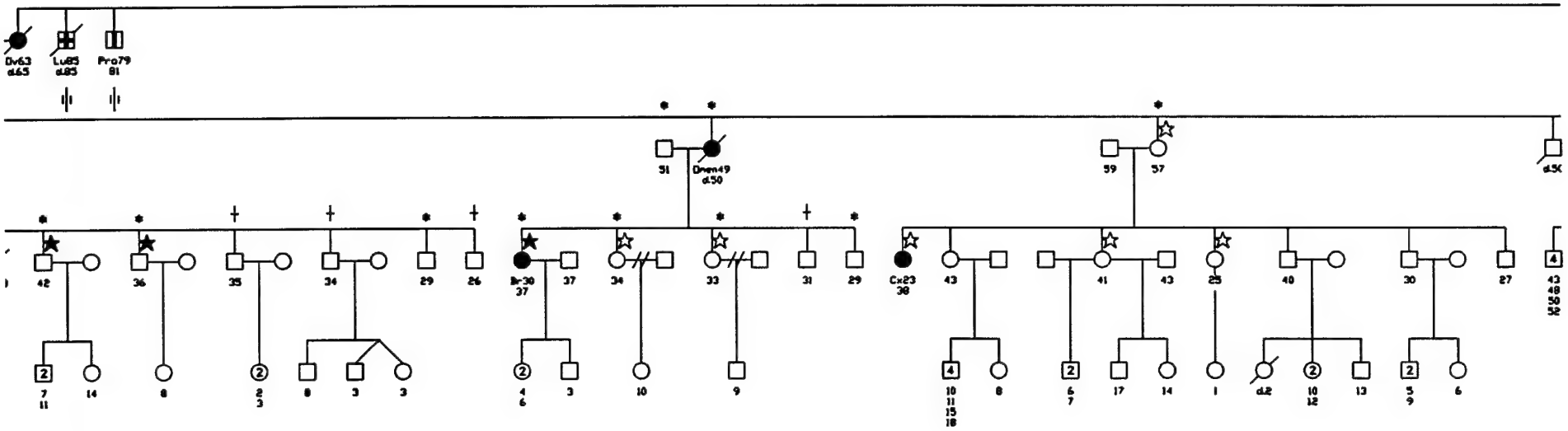
Family 1816


d.82
Dv46
d.67
86
90
82
85
Lu53
d.54
71
d.68
Cx48
76
56
53
55
51
49
39
44
46
48
43
46
42
48
32
d.16
46
49
53
Br41
d.50
45
45
44
35
42
45
40
46
Br38
d.46
75
Dv49
d.52
23
Thy20
21
23
16
18
24
25
25
23
26
20
48
46
21
23
20

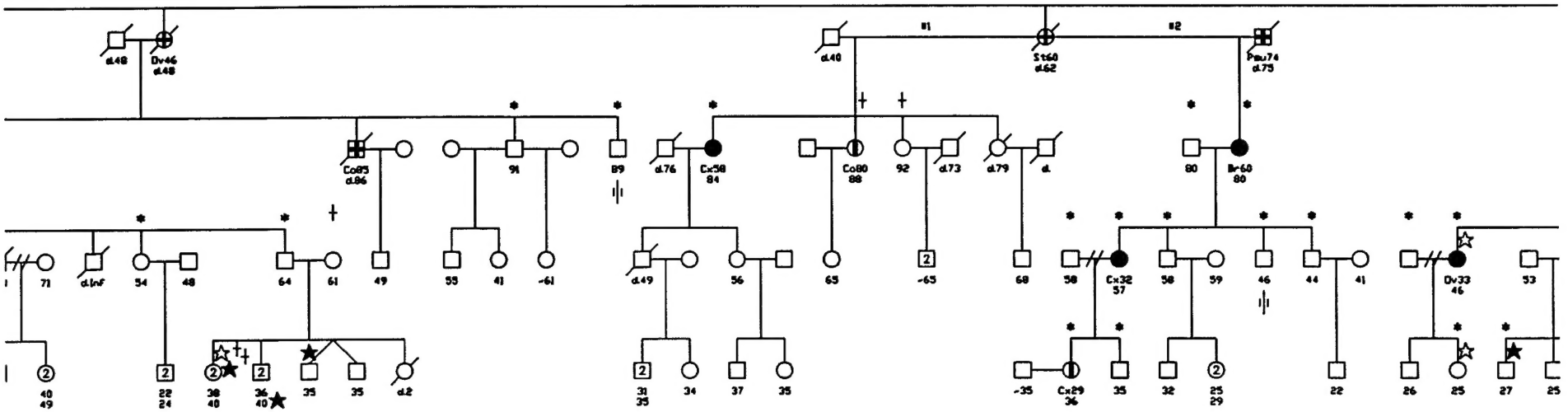
Family 1816


Lu82
d82
67
Pau44
d44
51
Br35
50
66
Br57
d59
43
Br32
39
46
44
32
39
36
36
Br35
41
48
49
27
29
32
33
40
39
38
31
30
24
44
43
16
13
9
14
21
17
19
2
7
10
2
9
11
14
4
18
22
24
26
2
6
8
7
12
9
3
16
17
18
4
6
7
15
11
8
6
3
18
20
22
19
2
19
20
16

Family 1816


Dv63
d65
Lu85
d85
Pro79
81
51
Dren49
d50
59
57
d5X
42
36
35
34
29
26
Br30
37
37
34
33
31
29
Cx23
38
43
41
43
25
40
30
27
43
48
58
52
7
11
14
8
2
3
8
3
3
4
6
3
10
9
10
11
15
18
8
6
7
17
14
1
d12
10
12
13
5
9
6

Family 1816



LEGEND

Male 1 / Female 2

- Individual number
- Unaffected
- Current age (e.g. 28 / 33)
- Cancer by Pathology, age at diagnosis, Current age (e.g. Lu53 / 55; Br45 / 47)
- Cancer by Family History, age at death (e.g. d.54 / d.86)
- Multiple Primary Cancers Unverified
- Multiple Primary Cancers by Medical Records or Death Certificates
- Multiple Primary Cancers by Pathology
- Cancer by Death Certificate or Medical Records
- Number of Unaffected Progeny (Both Sexes) (e.g. 4)
- Proband
- Twins
- Identical Twins

Cancer Sites

Bl	Bladder
Br	Breast
Co	Colon
Csu	Cancer Site Unknown
Cx	Cervix
Gb	Gallbladder
Leu	Leukemia
Lu	Lung
Mmel	Malignant Melanoma
Omen	Omentum
Ov	Ovarian
Psu	Primary Site Unknown
St	Stomach

- Blood Sampled
- Blood Kit sent
- Counseled in 1992
- Counseled in 1995

08/10/1995
1816-41

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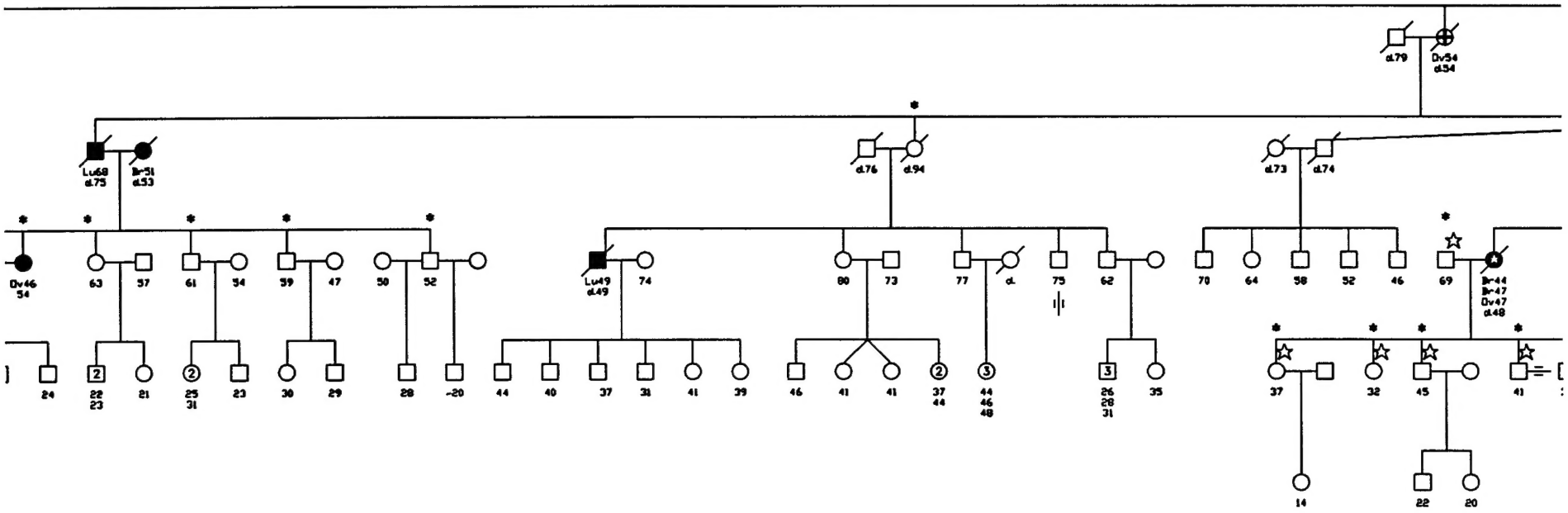
Family 1816


d.79
Dv54
d.54
Lu68
d.75
Br31
d.53
d.76
d.94
d.73
d.74
Dv46
54
63
57
61
54
59
47
50
52
Lu49
d.49
74
80
73
77
d.
75
62
70
64
58
52
46
69
Br44
Br47
Dv47
d.48
24
22
23
21
25
31
23
30
29
28
-20
44
40
37
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41
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37
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45
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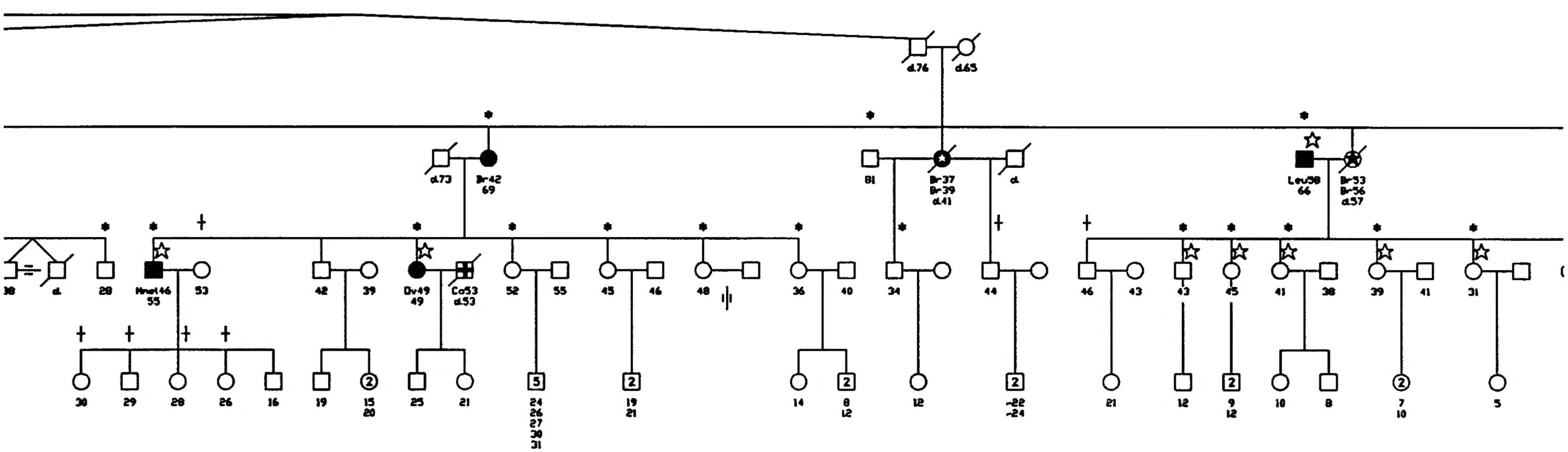
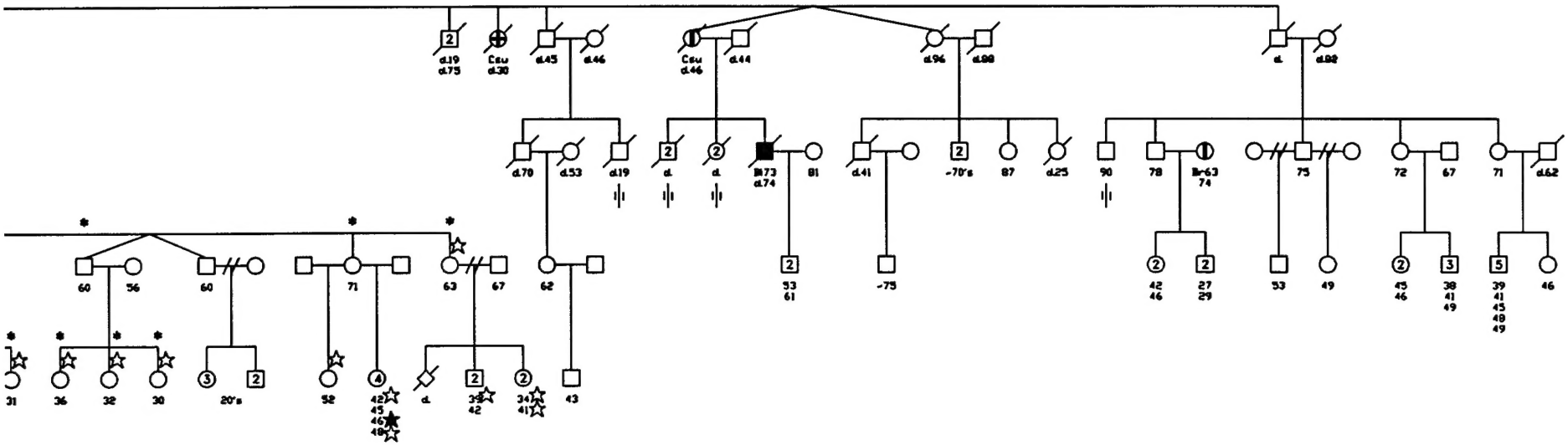
14
22
20

Family 1816


d.76
d.65
d.73
Br42
69
81
Br37
Br39
d.41
d.
Leu58
66
Br53
Br56
d.57
Hmal46
55
Dv49
49
Co53
d.53

Family 1816


d.19
d.75
Csu
d.30
d.45
d.46
Csu
d.46
d.44
d.96
d.98
d.
d.82
d.70
d.53
d.19
d.
d.
Br73
d.74
81
d.41
~70's
87
d.25
90
78
Br63
74
75
72
67
71
d.62
60
56
60
71
63
67
62
33
61
~75
42
46
27
29
33
49
45
46
38
41
49
39
41
45
48
49
46
31
36
32
30
20's
52
42
45
46
48
d.
34
41
43